IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Aomatsu et al.	EXAMINER:	Kwon, Brian Yong S
SERIAL NO.:	09/674,815	ART UNIT:	1614
FILED:	12/07/2000	CONFIRMATION NO.:	5030

FOR: STABILIZED PHARMACEUTICAL PREPARATION CONTAINING 4-AMINO-3-SUBSTITUTED-BUTANOIC ACID DERIVATIVES AND PROCESS FOR PREPARING THE SAME

APPEAL BRIEF TO THE BOARD OF PATENT APPEALS AND INTERFERENCES, PURSUANT TO 37 CFR § 41.37

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

This Brief to the Board of Patent Appeals and Interferences is submitted, under 37 CFR §41.37 in support of Applicants appeal of a Final Office Action mailed December 1, 2006. Applicant submitted an After-Final amendment and a Notice of Appeal on April 2, 2007, making the Appeal Brief due on or before Saturday June 2, 2007. An Advisory Action was not provided. Applicant is timely submitting this appeal brief on Wednesday May 30, 2007.

The Commissioner is authorized to charge the $500.00 Appeal Brief fee (37 CFR §41.20(b)(2)) to Deposit Account 16-1445. If additional charges are required with the filing of this Brief, Applicant authorizes the Commissioner to charge the fee to the same deposit account.

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(1) Real Party in Interest

The real party in interest of the above-referenced application is Pfizer Inc, a U.S. Corporation organized under the laws of the State of Delaware and having its headquarters at 235 East 42nd Street, New York, New York, by virtue of assignment from the inventor to the Warner-Lambert Company dated April 2, 1999 and recorded in the U.S. Patent and Trademark Office on April 22, 1999 at reel number 9907 and frame number 0153. Assignee Warner-Lambert Company is a wholly owned subsidiary of Pfizer Inc.

(2) Related Appeals and Interferences

There are no other appeals or interferences presently pending for application 09/674,815 which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant pending appeal.

(3) Status of the Claims

Claims 34-38 were rejected in a Final Office Action mailed December 1, 2006 in response to an amendment filed September 28, 2006. Claim 34 is an independent claim. Claims 35-38 are dependent claims. Therefore, claims 34-38 are pending in this appeal. The appealed claim set is provided in the Claims Appendix of this paper.

(4) Status of Amendments

A Final Office action was mailed December 1, 2006 which rejected claims 34-38. Applicant submitted an After Final amendment on April 2, 2007, wherein Applicant amended independent claim 34, dependent claim 38, and added new claim 40. Further, Applicant simultaneously submitted a Notice of Appeal. Despite telephone discussions with the Examiner, the Office did not send out an Advisory Action indicating that the After Final Amendment would be entered for purposes of this appeal. Therefore, Applicant has submitted those claims as presented on September 28, 2006, in lieu of those in the After Final Amendment of April 2, 2007.

(5) Summary of Claimed Subject Matter

Independent claim 34 of the present invention is drawn to a solid pharmaceutical composition (PCT/US99/10190; page 22, line 19-20) comprising a neutral alpha-amino acid (PCT/US99/10190; page 44, line 12), a compound selected from gabapentin and pregabalin (PCT/US99/10190; page 42, line 8), wherein the pharmaceutical composition is a solid (PCT/US99/10190, page 22, line 19-20). Claims 35-38 depend from claim 34. Compositions of the present invention exhibit significantly improved physical stability during storage, as manifested by a reduced tendency of the drug, gabapentin or pregabalin, to form a lactam impurity.

(6) **Grounds of Rejection to be Reviewed on Appeal**

The issues on appeal are (a) whether the composition of claims 34-38 are obvious under 35 U.S.C. §103(a) over Robson et al. (US 4126684) in view of Costa et al. (US5248678), and further in view of Bays et al. (WO 96/11680); and (b) whether claims 34-38 are patentable under the judicially created doctrine of double patenting over claims 36-37 of co-pending US Application No. 09/674,819.

(7) Argument

Claims 34-38 stand rejected as of the Final Office Action mailed December 1, 2006. A Notice of Appeal was filed and received electronically on April 2, 2007. Applicant submits the following arguments to overcome the Office's final rejection.

a) Rejection of claims 34-38 under 35 USC §103(a).

The Final Office Action rejected claims 34-38 as being obvious under 35 U.S.C. §103(a) over Robson et al. (US 4126684, hereinafter "Robson", Exhibit A) in view of Costa et al. (US5248678, hereinafter "Costa", Exhibit B), and further in view of Bays et al. (WO 96/11680, hereinafter "Bays", Exhibit C). Applicant asserts that the claims are patentable over Robson in view of Costa and Bays. Claims 34-38 are drawn to a stable

solid pharmaceutical composition comprising a neutral alpha-amino acid and gabapentin or pregabalin. Applicant respectfully submits that the rejection, as applied to claims 34-38, is improper because (1) it does not establish a prima facie case of obviousness, and (2) the Office has disregarded data in the specification that shows that the claimed compositions achieve surprising and unexpected results.

(1) Prima Facie Obviousness

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to a skilled artisan, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed Cir. 1991). Applicant respectfully submits that there is no suggestion or motivation to combine Robson, Costa, and Bays, there is no reasonable expectation of success, and for reasons of record and further reasons detailed below, the Office has not met its burden of establishing a prima facie case of obviousness. Therefore, the rejection is improper.

Applicant respectfully submits that there is no motivation to modify the references or to combine the references. The claimed invention relates to a stable pharmaceutical composition comprising a neutral alpha-amino acid, and gabapentin or pregabalin. According to the Office action, Robson et. al., discloses a composition comprising a 4-amino-3-substituted butanoic acid derivative such as baclofen, alpha amino acid glycine, auxiliary agent (i.e., sorbitol, mannitol, lactose, etc.,) and aqueous gelatin solution, wherein said composition is prepared in various dosage forms including tablet, capsule, and solution.

Applicant submits that there is no motivation to modify Robson because to do so would render Robson unsuitable for its intended purpose. If proposed modification

would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed Cir. 1984). The purpose of Robson is to reduce either the addiction liability of an addicting agent or the withdrawal symptoms caused by it by administering a composition comprising a) an addicting amount of a barbiturate and a narcotic agent, b) a 4-amino-3-p-halphenylbutyric acid, and c) a pharmaceutical excipient. A key element of the Robson claim is the addicting amount of a barbiturate and a narcotic agent. Applicant submits that the pharmaceutical composition of the instant invention only comprises gabapentin or pregabalin as active agents and does not permit the inclusion of a barbiturate and narcotic agent. Eliminating the barbiturate and narcotic agent in Robson to arrive at Applicant's invention would render Robson unsuitable for its intended purpose and therefore Robson cannot be used to render the present invention obvious.

Moreover, Robson provides a general listing of pharmaceutical excipients including: diluents (e.g. lactose, sucrose, mannitol, sorbitol, cellulose, and glycine); lubricants (e.g. silica, talc, stearic acid, and polyethylene glycol); binders (e.g. silicates, starch paste, gelatin, and methylcellulose); disintegrants (e.g. starches, agar, sodium salt, and enzymes of the binders or effervescent mixtures); and absorbents, colorants, flavors, and sweeteners; all of which are compatible substances normally used in preparing pharmaceutical formulations. However, Robson does not provide any indication that the broad list of suitable excipients could in and of themselves prevent lactamization of gabapentin or pregabalin. At most, Robson only represents an "obvious to try rationale," which cannot render the claims obvious. *In re Geiger*, 815 F.2d at 688, 2 USPQ2d at 1278; *In re Yates*, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed Cir 1988); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1986) – cert. denied 107 S.Ct. 1606, 94 L.Ed.2d. 792 (1987). Robson provides numerous choices of pharmaceutical excipients for the manufacture of a pharmaceutical formulation, but does not provide any guidance for determining whether any particular

combination of excipients or whether a specific excipient will stabilize the drug product. As such, there is no teaching or suggestion or reasonable expectation of success provided by Robson to manufacture a stable solid dosage form.

Further, the combination of familiar elements, e.g. pharmaceutical excipients, would be construed as obvious when it does no more than yield predictable results. However, the instant invention has shown that the addition of a neutral alpha amino acid stabilizes the drug product from forming a lactam. This stabilizing effect was not known and would not be predictable. Therefore, since the combination of familiar elements according to known methods would not yield a predictable result, the instant invention cannot be said to be obvious. *KSR Intl Co. v Teleflex Inc.*, 127 S.Ct. 1727, 2007, WL 1237837, at 12 (2007).

Further, the Examiner supplied references Costa et al., and Bays et al., to demonstrate that the art recognized the functional equivalent of gabapentin and baclofen as a GABA agonist. Costa et al discloses the administering of effective amounts of an adenosine receptor agonist in combination with a GABA agonist to increase alertness or arousal in a comatose or near-comatose patient. Bays et al., describes the use of GABA agonists for the treatment of emesis. Neither Costa nor Bays provide any motivation or suggestion to formulate gabapentin or pregabalin with an alpha amino acid. Thus, neither of them alone or in combination provide any teaching, suggestion, or motivation, relative to Robson, et al., to formulate a stable solid pharmaceutical composition for gabapentin or pregabalin.

(2) Surprising and Unexpected Results

Applicant respectfully submits that the Office has disregarded the surprising and unexpected results of the addition of an alpha amino acid on the stability of gabapentin and pregabalin. As disclosed in the specification, one particular problem with which Applicant was concerned is degredation of gabapentin or pregabalin into corresponding lactam in the drug product. Applicant has discovered that the addition of a neutral alpha amino acid can prevent formation of lactam (lactamization). The data provided in the

specification, pages 43-53, show that the addition of an alpha amino acid reduces the amount of lactamization. For example, Table 3 (pg. 44) shows that the addition of glycine or L-valine decreased the amount of gabapentin lactamization by about 60%. Further, Table 10 (pg. 52) shows that the addition of glycine and L-valine decrease pregabalin lactamization by about 50%. These results are surprising and unexpected. Nothing in the references cited teach or suggest the stabilizing affect of an alpha amino acid on gabapentin or pregabalin, and therefore, Applicant respectfully requests that the obviousness rejection be withdrawn and the claims be allowed to grant.

b) Rejection of claims 34-38 under the judicially created doctrine of double-patenting

The Examiner has maintained the rejection to Claims 34-38 under the judicially created doctrine of double patenting over claims 36-37 of co-pending US Application No. 09/674,819. Double patenting results when the right to exclude granted by a first patent is unjustly extended by the grant of a later issued patent or patents. *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982). Applicants previously submitted that the non-statutory double patenting rejection was improper because US Application No. 09/674,819 had not yet issued as a patent and no actual double patenting rejection may be properly made over claims of a co-pending application. Thus, if this is the only remaining rejection in the current application, the Office should withdraw the rejection and allow the application to issue as a patent.

c) **Conclusion**

Applicant respectfully requests that the finality of the §103(a) and judicially created doctrine of double-patenting be withdrawn and that the claims of the present invention be allowed to issue.

(8) Claims Appendix

1-33. (Canceled).

34. (Previously presented). A pharmaceutical composition comprising:
(a) a neutral α amino acid, and
(b) a 4-amino-3-substituted-butanoic acid derivative selected from the group consisting of gabapentin and pregabalin, wherein the pharmaceutical composition is a solid.

35. (Previously presented). The composition of Claim 34, wherein the neutral α-amino acid is one or more selected from: glycine, phenylglycine, hydroxyphenylglycine, dihydroxyphenylglycine, L-alanine, hydroxy-L-alanine, L-leucine, hydroxy-L-leucine, dihydroxy-L-leucine, L-norleucine, methylene-L-norleucine, L-ketonorleucine, L-isoleucine, hydroxy-L-isoleucine, dihydroxy-L-isoleucine, L-valine, hydroxy-L-valine, L-isovaline, L-norvaline, hydroxy-L-norvaline, hydroxy-L-ketonorvaline, L-methionine, L-homomethionine, L-ethionine, L-threonine, acetyl-L-threonine, L-tryptophan, hydroxy-L-tryptophan, methyl-L-tryptophan, L-tyrosine, hydroxy-L-tyrosine, methyl-L-tyrosine, bromo-L-tyrosine, dibromo-L-tyrosine, 3,5-diiodo-L-tyrosine, acetyl-L-tyrosine, chloro-L-tyrosine, L-m-tyrosine, L-levodopa, L-methyldopa, L-thyroxine, L-serine, acetyl-L-serine, L-homoserine, acetyl-L-homoserine, ethyl-L-homoserine, propyl-L-homoserine, butyl-L-homoserine, L-cystine, L-homocystine, methyl-L-cysteine, allyl-L-cysteine, propyl-L-cysteine, L-phenylalanine, dihydro-L-phenylalanine, hydroxymethyl-L-phenylalanine, L-aminobutyric acid, L-aminoisobutyric acid, L-ketoaminobutyric acid, dichloro-L-aminobutyric acid, dihydroxy-L-aminobutyric acid, phenyl-L-aminobutyric acid, L-aminovaleric acid, L-aminohydroxyvaleric acid, dihydroxy-L-aminovaleric acid, L-aminoisovaleric acid, L-aminohexanoic acid, methyl-L-aminohexanoic acid, L-aminoheptanoic acid, L-aminooctanoic acid, and citrulline, and the D- and DL-forms thereof.

36. (Previously presented). The composition of Claim 35, wherein the neutral α-amino acid is one or more selected from:
glycine, phenylglycine, hydroxyphenylglycine, dihydroxyphenylglycine, L-alanine, hydroxy-L-alanine, L-leucine, hydroxy-L-leucine, dihydroxy-L-leucine, L-isoleucine, hydroxy-L-isoleucine, dihydroxy-L-isoleucine, L-valine, hydroxy-L-valine, L-isovaline, and the D- and DL- forms thereof.

37. (Previously presented). The composition of Claim 34, wherein a total amount of the neutral α-amino acid is in the range of 0.001 - 80 moles per mole of the 4-amino-3-substituted-butanoic acid derivative.

38. (Previously presented). The composition of Claim 34, wherein the 4-amino-3-substituted-butanoic acid derivative is gabapentin.

39. (Canceled).

(9) Evidence Appendix

a) Exhibit A - US 4,126,684 (Robson, et al.)

b) Exhibit B - US 5,248,678 (Costa, et al.)

c) Exhibit C - WO96/11680 (Bays et al.)

(10) Related Proceedings Appendix

No related proceeding documents are enclosed for reasons set forth in (2) above.

Respectfully submitted,

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